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Patentanmeldung Nr. Patent application No. Demande de brevet n°

00811252.6

Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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R C van Dijk

DEN HAAG, DEN
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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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Method for processing a nucleic acid sample by swinging a segment of a cartridge wall, a system and a cartridge for performing such a method

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METHOD FOR PROCESSING A NUCLEIC ACID SAMPLE BY SWINGING A SEGMENT OF A CARTRIDGE WALL, A SYSTEM AND A CARTRIDGE FOR PERFORMING SUCH A METHOD

FIELD OF THE INVENTION

The present invention relates to a method for processing a nucleic acid sample contained in a liquid.

The invention further relates to a system for processing a nucleic acid sample contained in a liquid.

The invention further relates to a cartridge for processing a nucleic acid sample contained in a liquid.

The invention relates in particular to processing of a nucleic acid sample contained in a liquid introduced into a cartridge containing a chip shaped carrier having a biochemically active surface which is adapted to be read by an opto-electronic reading device.

BACKGROUND OF THE INVENTION

Within the context of the instant invention and in a preferred embodiment, a chip shaped carrier is a substrate, in particular a glass chip of e.g. squared shape having a thickness of e.g. 0.7 or 1.0 millimeter and a so called active surface, which is a surface coated with an array of different snippets of DNA or other molecular probes, e.g. DNA oligonucleotide probes, located at known positions on that surface. Those probes serve for detecting DNA fragments with a complementary DNA sequence.

Within the context of the instant invention and in a preferred embodiment the above- mentioned cartridge is in

focuses on determining the relationship between genetic sequences and human physiology.

For efficient use of a chip shaped carrier of the above described type it is necessary that the sample solution containing one or more targets to be sequenced effectively contacts the active surface of the chip shaped carrier. Moreover, in view of the relatively large number of sample solutions to be processed, this effective contact should be achieved with high reproducibility and at low cost.

Known prior art attempts to attain these aims require means for pumping a liquid containing a nucleic acid sample into and out a chamber of a cartridge in order to obtain the desired effective contact between the liquid containing the sample and the active surface of the chip shaped carrier. This approach is too expensive, cumbersome and requires too much working space, and can therefore not satisfy present day requirements on this kind of apparatuses.

A main aim of the instant invention is therefore to provide a method, a cartridge and a system which make it possible to provide effective contact of a solution processed in a cartridge of the above mentioned kind with the active surface of the chip shaped carrier and this with a high reproducibility and at low cost.

SUMMARY AND MAIN ADVANTAGES OF THE INVENTION

According to a first aspect of the invention the above aim is achieved with a method according to claim 1, with a system according to claim 2, and with a cartridge according to claim 3. Features of preferred embodiments are defined by the dependent claims.

Fig. 6 shows a system according to the invention for simultaneously handling a plurality of cartridges 42.

DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

As schematically represented in Fig. 1, a cartridge 42 according to the invention comprises a chamber 41 and chip shaped carrier 44.

Chip shaped carrier 44 has an active surface 45 which carries an array of oligonucleotides and which faces the inner surface of a wall 46 of cartridge 42.

Chamber 41 of cartridge 42 has a narrow interior and includes a channel 43. A portion of channel 43 lies between active surface 45 of chip shaped carrier 44 and the inner surface of wall 46.

As depicted in Fig. 1 cartridge 42 comprises a channel plate 51 which comprises and essentially defines the shape of chamber 41 and channel 43, and a chip plate 52 which is adapted to receive and hold chip shaped carrier 44 at the position shown in Fig. 1 within a cavity 53 of chip plate 52.

When channel plate 51 and chip plate 52 are assembled together to form cartridge 42, this cartridge has an inlet which allows to introduce a predetermined volume of a liquid containing a nucleic acid sample into chamber 41 of cartridge 42 by means of a pipetting needle which is part of an automatic pipetting unit. Cartridge 42 also has an outlet which allows to remove said liquid sample from cartridge 42 if and when desired.

cartridge 42.

The means for positioning and fixing chip shaped carrier 44 into cavity 53 available in chip plate 52 are preferably those described in co-pending European patent application No. 00810501.7 entitled "Device for packaging a chip shaped carrier and process for assembling a plurality of such carriers" filed on June 8, 2000 by the applicant of this application.

Cartridge 42 has a structure which has in particular the following features:

A rigid segment 47 of wall 46 is adapted to be swung of a predetermined angle back and forth about a torsion bar 59 and with respect to an initial position at which wall segment 47 is coplanar with wall 46. In order to enable the latter swinging motion of rigid wall segment 47, this segment is connected by elastic wall segments 48 and 49 to the remaining part of wall 46

When wall segment 47 is swung in a first sense, one end of wall segment 47 is moved towards active surface 45, and when wall segment 47 is swung in a second sense opposite to the first sense, the latter end of wall segment 47 is moved away from active surface 45. The preferred size of the predetermined swinging angle lies between six and twelve degrees. This predetermined swinging angle is measured with reference to the position of wall segment 47 at which this segment is coplanar with wall 46.

In order to perform a method according to the invention cartridge 42 is inserted and thereby positioned into a cartridge holder 56 which is represented schematically in Fig. 1.

the above described features and comprises in addition means for swinging the above mentioned segment of wall 46 of a predetermined angle back and forth around a torsion bar 59 in order to cause relative motion of the liquid sample contained in channel 43 with respect to active surface 45 of chip shaped carrier 44. The means for swinging wall segment 47 comprise e.g. a step motor 63 and suitable drive means (belt 64 and pulleys 65 and 66) connecting this motor 63 to wall segment 47.

Fig. 2 shows in particular channel 43, rigid segment 47 of wall 46, torsion bar 59.

Channel plate 51 is a two-component part made by injection molding which is composed of a hard channel plate and a soft thermoplastic material, e.g. an elastomer which has several functions as part of cartridge 42. Plugs 62 and 63 seal and thereby separate channel 43 from its environment. Plug 62 is pierced by a first hollow needle for introducing or removing a liquid into channel 43. During such steps plug 63 is also pierced by a second hollow needle for venting channel 43. Plugs 62 and 63 effectively seal channel 43 even after being pierced several times by the hollow needles.

Elastic segments 48 and 49 of wall 46 are the portions of the elastomer material which undergo the largest deformation during use of the cartridge.

Chip plate 52 is also made by injection molding, and is preferably as well a two-component part. Cavity 53 of chip plate 52 is filled by chip shaped carrier 44 (not shown).

Fig. 3 shows an perspective exploded view of components of cartridge 42 seen from a point of view opposite to the one of Fig. 2. Fig. 3 shows in particular torsion bar 59 about

According to a preferred embodiment of the invention a method of the type just described is carried out simultaneously on a plurality of cartridges by means of a system according to the invention adapted for that purpose as shown by Fig. 6.

A typical use of a method, cartridge and system according to the invention is for carrying out process steps of a so called post PCR processing of a liquid containing a nucleic acid sample which has been amplified by means of a PCR method or the like.

Such post PCR processing carried out using cartridge 42 includes in general terms the following steps: introducing liquid into chamber 41 and into channel 43 of cartridge 42 at some points of time and withdrawing liquid from chamber 41 and channel 43 of cartridge 42 at other points of time, repeating this steps several times, and heating and cooling cartridge 42 during predetermined time intervals according to predetermined temperature profiles, e.g. in a temperature range between zero and seventy degrees Celsius. The liquid containing the nucleic acid sample being one of the liquids introduced into and withdrawn from cartridge or 42, another type of liquid handled in this way as part of the method being e.g. buffer liquid used for rinsing chamber 41 and channel 43 during rinsing steps mentioned hereinafter.

More in detail a post PCR processing of an amplified nucleic acid sample using the devices described above comprises e.g. the following steps:

5) Stain hybridization

In this step a fluorescent solution is added to the liquid containing a sample contained in the cartridge in order that individual fluorescing molecules can get attached to DNA fragments. During this step the cartridge is kept again at a higher temperature level.

6) Stain rinse

In this step remaining free fluorescing molecules are washed out of the cartridge by means injecting a washing buffer through an inlet of the cartridge at a suitable first position thereof and changing the position cartridge to a second position at which liquid carrying those free fluorescing molecules is withdrawn from the cartridge through an outlet thereof. This step is repeated up to ten times.

7) Detection

After step 6) the sample is bound to the active surface 45 of chip shaped carrier 44, this surface is flooded with a sample-free buffer, and the cartridge containing the liquid containing a sample is transferred by suitable transport means which include a gripper to a detection unit, where the surface of the active surface of chip shaped carrier is scanned with a laser beam and fluorescent light emerging from said active surface in response to that excitation is measured by means of suitable instrument. In order that this detection can be performed the cartridge has an opening through which the chip shaped carrier and the active surface thereof are accessible to opto-electronic examination.

Modifications and alternative embodiments of the invention will be apparent to those skilled in the art in view of the foregoing description. Accordingly, this description is to be construed as illustrative only and is for the purpose of teaching those skilled in the art the best mode of carrying out the invention. Details of the apparatus and of the method described may be varied without departing from the spirit of the invention and the exclusive use of all modifications which come within the scope of the appended claims is reserved.

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Claims

1. A method for processing a nucleic acid sample contained in a liquid, said method comprising

(a) introducing said sample into a chamber (41) of a cartridge (42) which contains a chip shaped carrier (44) having an active surface (45) which carries an array of oligonucleotides, said active surface (45) facing the inner surface of a wall (46) of said cartridge,

said chamber (41) having a narrow interior and including a channel (43), a portion of said channel lying between said active surface (45) of said chip shaped carrier (44) and the inner surface of said wall (46),

a rigid segment (47) of said wall (46) being adapted to be swung of a predetermined angle back and forth about a torsion bar (59), swinging of that segment (47) in one sense moving one end thereof towards said active surface (45), and swinging of that segment (47) in the opposite sense moving said one end of that segment (47) away from said active surface (45),

(b) positioning said cartridge (42) into a cartridge holder (36) which holds said cartridge, said positioning being effected before or after introduction of said sample into said chamber (41), and

(c) swinging said rigid segment (47) of said wall (46) of said predetermined angle back and forth about said torsion bar (59) in order to cause relative motion of the liquid sample contained in said channel (43) with respect to said active surface (45) of said chip shaped carrier (44).

4. A cartridge for processing a nucleic acid sample contained in a liquid, said cartridge comprising

(a) a chip shaped carrier (44) having an active surface (45) which carries an array of oligonucleotides, said active surface (45) facing the inner surface of a wall (46) of said cartridge,

(b) a chamber (41) having a narrow interior and including a channel (43), a portion of said channel lying between said active surface (45) of said chip shaped carrier (44) and the inner surface of said wall (46), and

(c) a rigid segment (47) of said wall (46) being adapted to be swung of a predetermined angle back and forth about a torsion bar (59), swinging of said segment (47) in one sense moving one end thereof towards said active surface (45), and swinging of said segment (47) in the opposite sense moving said one end of that segment (47) away from said active surface (45).

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Abstract

A method for processing a nucleic acid sample contained in a liquid comprises: (a) introducing said liquid into a chamber (41) of a cartridge (42) which contains a chip shaped carrier (44) having an active surface (45) which carries an array of oligonucleotides, said active surface (45) facing the inner surface of a wall (46) of said cartridge,

said chamber (41) having a narrow interior and including a channel (43), a portion of said channel lying between said active surface (45) of said chip shaped carrier (44) and the inner surface of said wall (46),

a rigid segment (47) of said wall (46) being adapted to be swung of a predetermined angle back and forth about a torsion bar (59), swinging of that segment (47) in one sense moving one end thereof towards said active surface (45), and swinging of that segment (47) in the opposite sense moving said one end of that segment (47) away from said active surface (45),

(b) positioning said cartridge (42) into a cartridge holder (56) which holds said cartridge, said positioning being effected before or after introduction of said liquid containing a sample into said chamber (41), and

(c) swinging said rigid segment (47) of said wall (46) of said predetermined angle back and forth about said torsion bar (59) in order to cause relative motion of the liquid contained in said channel (43) with respect to said active surface (45) of said chip shaped carrier (44).

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(Figure 1)

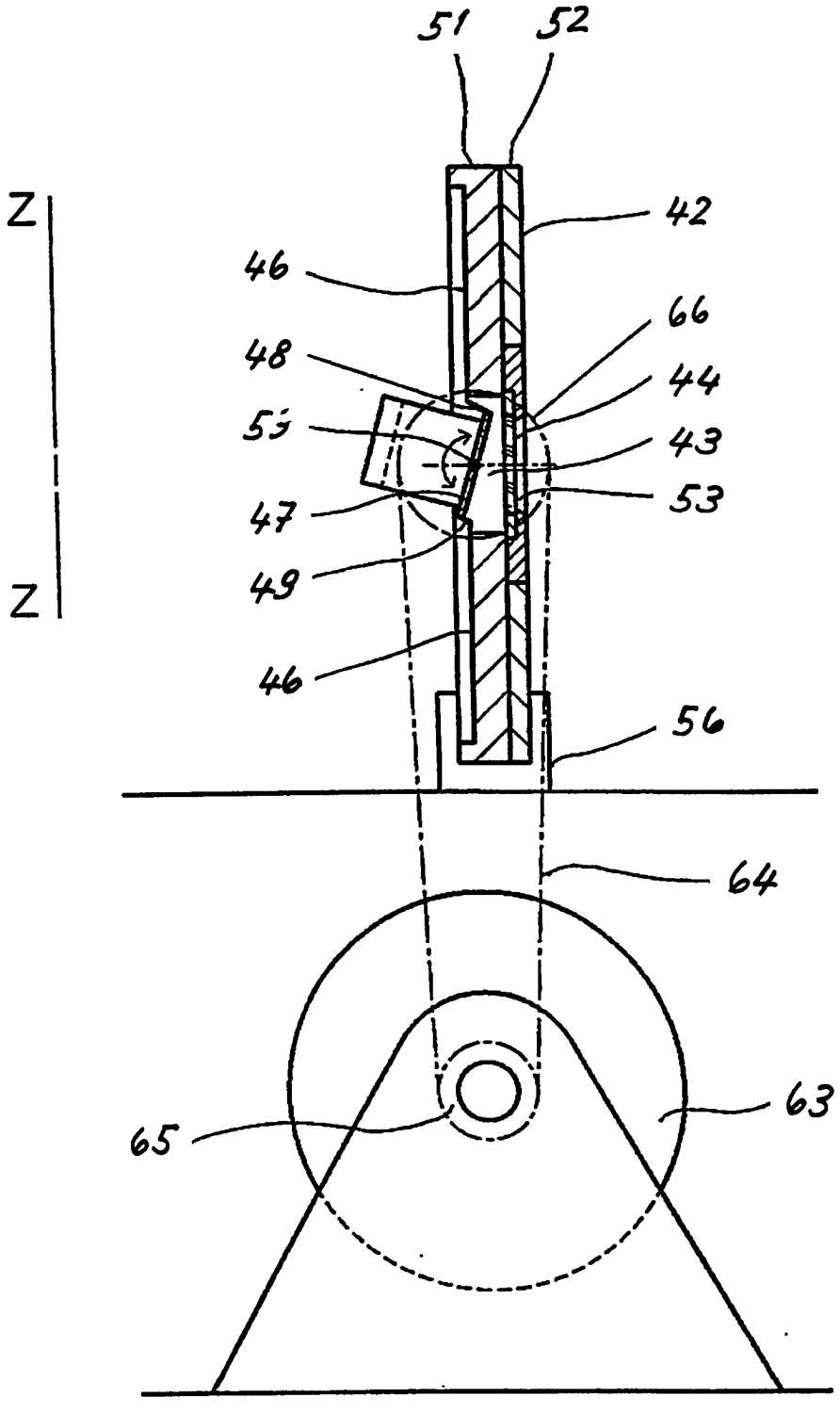

Fig. 1

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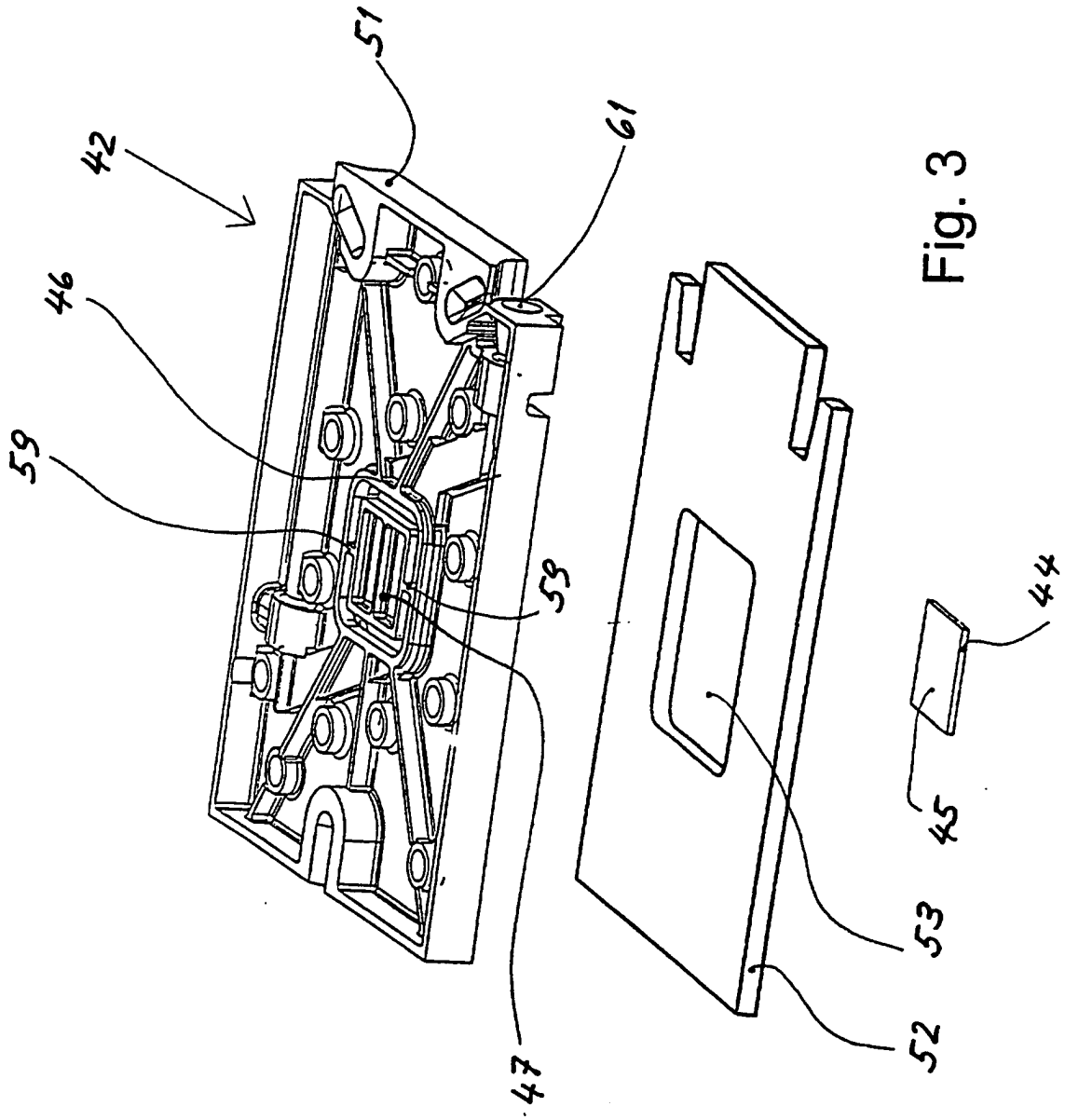

Fig. 3

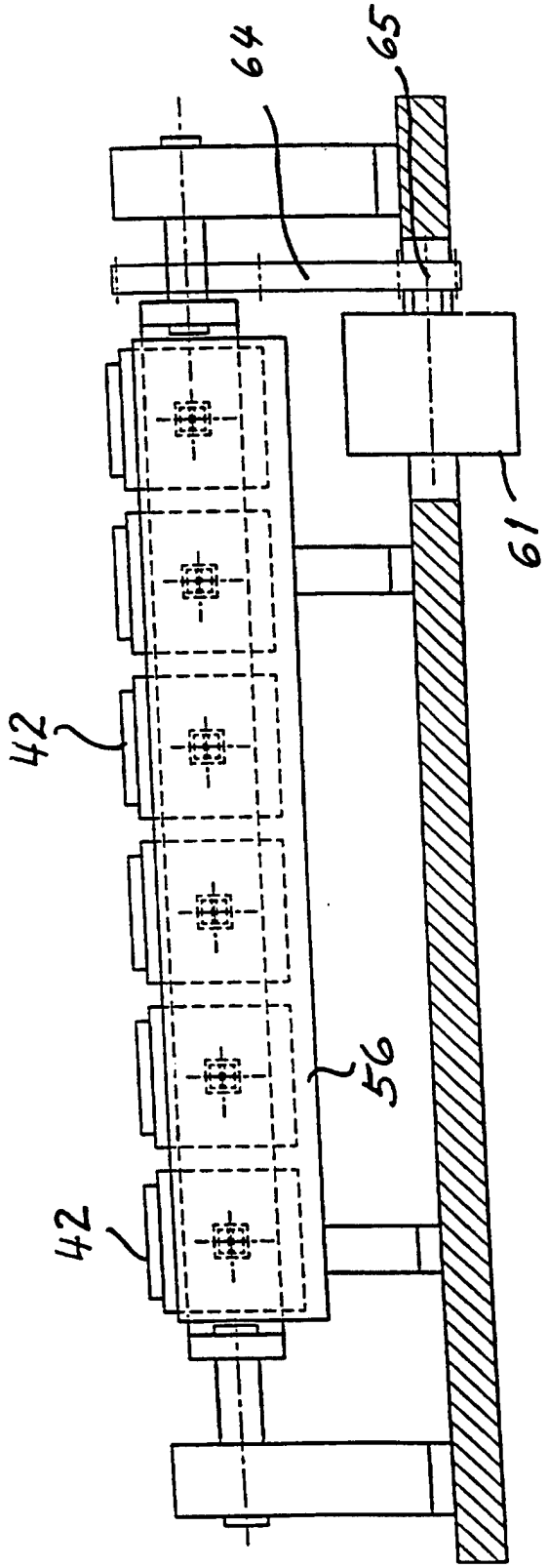

Fig. 6